



Walter Reed Army Institute of Research Dengue Vaccine Program

Both dengue fever (DF) and dengue hemorrhagic fever (DHF) are mission-stopping disease threats to U.S. forces deployed throughout the tropics and subtropics. DF is endemic in many tropical and subtropical regions of the world where military personnel are stationed or may deploy, including Central and South America, the Caribbean, Southeast Asia, Africa, northeastern Australia and the Western and Southern Pacific Region. Dengue epidemics are explosive, with a high morbidity (illness) and the potential to rapidly incapacitate large numbers of personnel in a short period of time. It has been estimated that there are 20 million cases of dengue infection resulting in around 24,000 deaths each year. In Southeast Asia, DF rivals malaria as a killer of children. The case-fatality rate of DHF is approximately 5 percent.

DF is a prostrating acute febrile viral infection characterized by sudden onset of fever, severe headache, pain behind the eyes which worsens with eye movement, generalized joint and muscle aches, lack of appetite, gastrointestinal disturbances, and rash. DHF is characterized by symptoms similar to DF, with the addition of systemic hemorrhage and shock. Recovery may be associated with prolonged fatigue and depression. Dengue fever and DHF have a geographical occurrence similar to malaria.

The primary vector for both DF and DHF throughout the tropical and subtropical world is *Aedes aegypti* an urban mosquito that has adapted to utilizing man-made containers for breeding, feeds almost exclusively on humans, and rests in secluded indoor sites where conventional insecticide spraying is ineffective. Unlike malaria, which is spread most often by the *Anopheles* spp. mosquitoes, DF tends to have a more urban distribution which has resulted in its increased occurrence compared to that of malaria as the world's population grows increasingly urban.

DF and DHF are caused by one of four closely related viral serotypes of the genus *Flavivirus*. The single-stranded RNA *Flavivirus* genus includes, in addition to the dengue virus, the yellow fever virus, the West Nile virus, the Japanese encephalitis virus, the tick-borne encephalitis virus, and others for a total of around 50 different virus species. Major Walter Reed, M.D., our institution's namesake, was a U.S. Army physician who first confirmed (in 1900) the transmission of yellow fever to humans was by a mosquito vector.

The four serotypes of dengue virus, known as dengue types DEN-1, DEN-2, DEN-3, and DEN-4, are prevalent viral diseases and have produced significant epidemics to the point of impeding mission accomplishment in U.S. military forces during combat operations. There are no vaccines or drugs to prevent disease caused by the dengue virus. The goal of this Program Area is to conduct basic and applied research leading to the development of a dengue vaccine.

Although research into the development of a dengue vaccine has been ongoing since the 1940's, the occurrence of dengue's four serotypes has repeatedly stymied research efforts. Individuals initially infected by one serotype gain immunity only to future infections by that serotype while paradoxically being put at greater risk of developing the more severe DHF with future infection by one of the other three serotypes. In the past, subsequent infection with different serotypes has been rare due to the different geographical distribution of the four serotypes. Now with the increase in world-wide human mobility there is an increased risk of subsequent infection with one of the different serotype. Ninety percent of the DHF patients can be shown to have had a previous infection with one of the other three serotypes. The dengue virus has also undergone genetic changes over the past few decades resulting in more pathogenic strains. These factors plus the difficulties in growing the dengue virus in tissue cultures and the lack of a suitable animal model has slowed research considerably.

The main problem with developing a trivalent (all four serotypes) vaccine has been with the incorporation of the DEN-3 serotype. Addition of the DEN-3 serotype has interfered with production of antibodies to the other three serotypes until WRAIR succeeded in attenuating it. A dengue tetravalent live attenuated vaccine (TLAV) previously developed and patented by a team of investigators from WRAIR is now considered one of the leading candidates to confer protection against all 4 dengue types. This vaccine is being further evaluated together with corporate partner GlaxoSmithKline in Phase 2 clinical trials in the U.S., Asia, and the Caribbean with the imminent goal of FDA licensure.